Review Article

Review on Potential Therapeutic Intervention of Diabetic Foot Disease

[1]Sharmistha Bhandari, [2] Tamalika Chakraborty*

[1]Department of Genetics, Master of Science, Guru Nanak Institute of Pharmaceutical Science and Technology, Kolkata, West Bengal, India.
[2]Department of Life Science, Assistant Professor, Guru Nanak Institute of Pharmaceutical Science and Technology, Kolkata West Bengal, India.
***Corresponding author's E-mail:** tamalika.chakraborty@gnipst.ac.in

Received: 18-01-2023; **Revised:** 26-02-2023; **Accepted:** 02-03-2023; **Published on:** 15-03-2023.

ABSTRACT

Individuals suffering from diabetes are at risk for developing ulcers in their lower extremities, which are sometimes aggravated by infection and place a heavy burden on their caretakers to prevent the dreaded need for amputation. While prompt and accurate antibiotic treatment directed at the causative organisms is a cornerstone of diabetic foot infection management, the rise in the number of multidrug-resistant organisms, such as methicillin-resistant Staphylococcus aureus as well as other multidrug-resistant Gram-negative species, has complex and difficult treatment recommendations. Due to the necessity of a comprehensive approach to wound treatment, the control over DFU is best handled by collaborating across disciplines to achieve the same goal. Scientific evidence suggests that DFU care should always include glucose monitoring, wound debridement, high-tech dressings, and offloading methods. In addition, in some circumstances, surgery to treat a chronic ulcer and prevent its return may be an integral part of the treatment plan. Healing of DFU can be accelerated with the use of a variety of adjunct treatments, including negative pressure wound therapy, hyperbaric oxygen therapy, bio-engineered skin, electrical stimulation as well as growth factors. Therefore, it is recommended that patients be educated on the need of maintaining regular foot care to prevent DFU and associated consequences.

Keywords: Diabetic foot; Diabetic ulcer; Wound management; Amputation; Foot care.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2023.v79i01.019

DOI link: http://dx.doi.org/10.47583/ijpsrr.2023.v79i01.019

INTRODUCTION

One of the complications of diabetes is the diabetic foot, the most severe and damaging complication of diabetes, manifesting as ulcers on the foot. There are three primary diabetes kinds which are diabetes of Type 1 Type 2, or gestational diabetes. Patients with Diabetes Mellitus (DM) are mostly impacted by foot ulcers, which is quite difficult. In reality, a diabetic foot ulcer is a type of full-thickness lesion that occurs most frequently distal to the ankle in diabetes individuals. In this diabetic patient, neuropathy and peripheral vascular disease of the lower extremity manifest as ulceration. In the diabetic population, diabetic foot ulcers occur between 4 and 10 percent of the time. Many estimates indicate that 5 percent of all diabetes patients develop foot ulcers, and the risk factors for diabetic patients have increased from 5 to 15 percent[1,2]. However, the majority of research focuses on the fact that risk variables commonly rise in the diabetes patient population [2]. Osteomyelitis is the name given to an infection of the bone that can occur in this type of incision. Charcot Neuropathy is a specific neuropathy illness involved in diabetic foot disease. Diabetic patients with foot complications are also likely to develop neuropathy, retinopathy, and problems with blood flow to the brain and the heart [3]. Estimates indicate that DFU contributes to 20% of hospital hospitalizations for DM patients[4]. If DFU is not treated properly, risks include sepsis, necrosis, loss of limb, or even mortality [4]. On the other side, once DFU has manifested, there is a greater likelihood that the ulcer may progress and necessitate amputation. Patients with DM have a 15-fold higher risk of amputation than those without the disease. DFU is believed to account for 50 to 70 percent of all lower limb amputations[5]. Each thirty seconds somewhere in the world, an amputation is performed because of DFU[6]. Moreover, DFU results in significant physical, emotional, and financial losses that have a detrimental influence on the quality of life[7].

If a diabetic patient's foot ulcer is not adequately treated, surface infections can spread to the hypodermis, eventually paralyzing muscles, tendons, bones, and joints. Recovery requires a minimum of two months, and nearly two-thirds of diabetic foot ulcers heal without surgical intervention. Diabetic foot ulcer and limb amputation are dependent upon the duration of diabetes and age. Vital is the eradication of diabetic foot ulcer, notwithstanding its detrimental influence on the patient's sense of self-worth. In the healthcare series, the financial burden of diabetic foot ulcer sufferers is discussed[8] Diabetic Foot is one of the most severe and damaging complications of diabetes, manifesting as ulcers on the foot. There are three primary diabetes kinds. Like – i. Type 1 diabetes, ii. Type 2 diabetes, iii. Gestational diabetes. Patients with Diabetes Mellitus are mostly impacted by foot ulcers, which is quite difficult.

In reality, a diabetic foot ulcer is a type of full-thickness lesion that occurs most frequently distal to the ankle in diabetes individuals. In this diabetic patient, neuropathy and peripheral vascular disease of the lower extremity manifest as ulceration. In the diabetic population, diabetic foot ulcers occur between 4 and 10 percent of the time. Many estimates indicate that 5 percent of all diabetes patients develop foot ulcers, and the risk factors for diabetic patients have increased from 5 to 15 percent [1,2]. However, the majority of research focuses on the fact that risk variables commonly rise in the diabetes patient population [2]. Osteomyelitis is the name given to an infection of the bone that can occur in this type of incision. Charcot Neuropathy is a specific neuropathy illness involved in diabetic foot disease. Patients with diabetic foot complications are also likely to develop neuropathy, retinopathy, ischemic heart disease, and cerebrovascular disease[3]. Estimates indicate that DFU contributes to 20% of hospital hospitalizations for DM patients[9]. If DFU is not treated properly, it can lead to infection, gangrene, amputation, and even death[4]. On the other side, once DFU has manifested, there is a greater likelihood that the ulcer may progress and necessitate amputation. The risk of lower limb amputation among DM patients is 15 times greater than among those without the condition. DFU is believed to account for 50 to 70 percent of all lower limb amputations[10]. In addition, it is reported that one limb is amputated due to DFU every 30 seconds worldwide[6]. Moreover, DFU results in significant physical, emotional, and financial losses that have a detrimental influence on the quality of life[7].

If a diabetic patient's foot ulcer is not adequately treated, surface infections can spread to the hypodermis, eventually paralyzing muscles, tendons, bones, and joints. Recovery requires a minimum of two months, and nearly two-thirds of diabetic foot ulcers heal without surgical intervention. Diabetic foot ulcer and limb amputation are dependent upon the duration of diabetes and age. Vital is the eradication of diabetic foot ulcer, notwithstanding its detrimental influence on the patient's sense of self-worth. In the healthcare series, the financial burden of diabetic foot ulcer sufferers is discussed[8] Diabetic Foot is one of the most severe and damaging complications of diabetes, manifesting as ulcers on the foot. There are three primary diabetes kinds. Like – i. Type 1 diabetes, ii. Type 2 diabetes, iii. Gestational diabetes. Patients with Diabetes Mellitus are mostly impacted by foot ulcers, which is quite difficult. In reality, a diabetic foot ulcer is a type of full-thickness lesion that occurs most frequently distal to the ankle in diabetes individuals. In this diabetic patient, neuropathy and peripheral vascular disease of the lower extremity manifest as ulceration. In the diabetic population, diabetic foot ulcers occur between 4 and 10 percent of the time. Many estimates indicate that 5 percent of all diabetes patients develop foot ulcers, and the risk factors for diabetic patients have increased from 5 to 15 percent [1,2]. However, the majority of research focuses on the fact that risk variables commonly rise in the diabetes patient population [2]. Osteomyelitis is the name given to an infection of the bone that can occur in this type of incision. Charcot Neuropathy is a specific neuropathy illness involved in diabetic foot disease. Patients with diabetic foot complications are also likely to develop neuropathy, retinopathy, ischemic heart disease, and cerebrovascular disease[3]. Estimates indicate that DFU contributes to 20% of hospital hospitalizations for DM patients[9]. If DFU is not treated properly, it can lead to infection, gangrene, amputation, and even death[4]. On the other side, once DFU has manifested, there is a greater likelihood that the ulcer may progress and necessitate amputation. The risk of lower limb amputation among DM patients is 15 times greater than among those without the condition. DFU is believed to account for 50 to 70 percent of all lower limb amputations[10]. In addition, it is reported that one limb is amputated due to DFU every 30 seconds worldwide[6]. Moreover, DFU results in significant physical, emotional, and financial losses that have a detrimental influence on the quality of life[7].

If a diabetic patient's foot ulcer is not adequately treated, surface infections can spread to the hypodermis, eventually paralyzing muscles, tendons, bones, and joints. Recovery requires a minimum of two months, and nearly two-thirds of diabetic foot ulcers heal without surgical intervention. Diabetic foot ulcer and limb amputation are dependent upon the duration of diabetes and age. Vital is the eradication of diabetic foot ulcer, notwithstanding its detrimental influence on the patient's sense of self-worth. In the healthcare series, the financial burden of diabetic foot ulcer sufferers is discussed [8].

Feet and Diabetes: Microbiology

Here, the most significant fact is that some microorganisms are responsible for this lethal infections[11]. Citron et al., who analyzed 427 culture-positive cases, found that only 16.2 percent had growth of a single species living microorganism, with the remainder of specimens being polymicrobial, and that 43.7% were sensitive to four or more species, confirming the occurrence of polymicrobial illnesses [12].

Mild to moderate infections often contain Gram-positive organisms, but moderate to serious infections are more likely to be polymicrobial, containing Gram-negative species, and more than half will have anaerobic organisms[13]. Anaerobes include organisms including Prevotella spp., *Bacteroides* spp., and *Peptostreptococcus* spp. Patients with ischemia of the foot or gangrene have an increased prevalence of anaerobic bacteria, although the full extent of their relevance is unknown[14]. While *S. aureus* has a reputation for being the most widespread pathogen, research from India indicates that Gram-negative aerobic organisms are more common. Bacteria belonging to the Gram-negative family, such as *Pseudomonas* spp. and Enterobacteriaceae, are commonly identified from cured illnesses. are commonly found in treated wounds that still have some moisture left[15]. The rise of methicillin-resistant *Staphylococcus aureus* (MRSA)

and extended-spectrum b-lactamases is a growing concern in healthcare and the population, respectively, but the latter presents a bigger challenge in developing countries due to the higher frequency of S. aureus infection there. Twenty to fifty percent of diabetics with infected or non-infected foot ulcers have MRSA[16], and its presence can significantly impede healing.

Table 1: Diabetic foot infections: a common source of pathogens

Bacteria	Pathogens
Gram-positive (Aerobic)	*Staphylococcus* spp. *Staphylococcus aureus* Coagulase-negative spp. *Enterococcus* spp. *Enterococcus faecalis* *Streptococcus* spp. *Streptococcus pyogenes* *Corynebacterium* spp.
Gram-negative (Aerobic)	*Proteus* spp. *Proteus mirabilis* *Klebsiella* spp. *Klebsiella pneumonia* *Klebsiella oxytoca* *Enterobacter* spp. *Enterobacter cloacae* *Pseudomonas aeruginosa* *Escherichia coli* *Morganella morganii*
Gram-positive (Anaerobic)	*Peptostreptococcus* spp. *Peptostreptococcus anaerobius* *Peptoniphilus asaccharolyticus*
Gram-negative (Anaerobic)	*Peptostreptococcus magna* *Bacteroides* spp. *Bacteroides fragilis* *Prevotella* spp. *Porphyromonas* spp.

Etiology of DFU

Several risk factors have been linked to the emergence of DFU in recent studies [17]. There are several possible threats, including Having diabetes for more than 10 years, being over the age of 60, having a high body mass index, and having several other medical conditions, including diabetic nephropathy, diabetic neuropathy, peripheral arterial disease, a high glycosylated hemoglobin level (HbA1c), foot disfigurement, high forefoot pressure, infections, and insufficient foot self-care, all increase the risk of foot problems in people with diabetes. Multiple studies have identified diabetes-related risk factors as intermediaries between foot and leg ulcers and amputations [18,19], however, the majority of DFUs have been caused by ischemia, neuropathic, or combination neuro ischemic abnormalities. Ten percent of DFU instances may be caused by ischemia alone, whereas the remaining ninety percent may be due to neuropathy alone or in conjunction with another ailment. Most diabetic foot clinics in the United Kingdom now see neuroischemic ulcers as the most prevalent kind of ulcer[20], indicating an increase in the prevalence of neuroischemic issues. Diabetics often experience issues with their feet due to peripheral sensory and autonomic neuropathy[21]. Ulcers, foot abnormalities, and shaky gait are all things that become more likely with this disorder.

Table 2: Risk factors for Ulceration

General or Systemic Contributions	Local issues
Rapidly rising blood sugar levels	Neuropathy of the Periphery
Period of diabetes	Deformity of the foot's structure
Damage to the blood vessels in the extremities	Misaligned footwear and traumatic experiences
Loss of sight or blindness	Callus
Kidney failure that persists over a long period	Evidence of previous amputation due to ulcer
Older age	Constantly high pressure
	Impairment of joint motion

Diabetic Neuropathy

According to the "International Consensus Group on Neuropathy," diabetic neuropathy is "the identification of symptoms of peripheral nerve injury in patients with diabetes after other probable causes of peripheral neuropathy have been ruled out"[22]. Minor nerve injury in diabetics might set off the development of foot ulcers. The risk of developing diabetic foot ulcers increases by a factor of seven in persons with peripheral diabetic neuropathy, according to studies[23].

"Distal Bilateral Symmetrical Neuropathy"

This kind of neuropathy is the most common symptom experienced by diabetics. Lower limbs are typically the first to be afflicted, while upper limbs are not immune. Nerve dysfunction worsens gradually from its distal to its proximal manifestations[22].

Distal symptoms of diabetic neuropathy are among the spectrum of possible presentations. Patients may experience hyperalgesia (a heightened feeling of pain following the administration of painful stimuli), lancinating pain, numbness or tingling, burning or prickling, as well as allodynia (contact pain or pain perception due to a non-

painful stimulus). Intense cramping that doesn't let up even while you're at rest is one symptom of a condition called restless leg syndrome[24]. Denervation of the muscles can occur when not only sensory nerve fibers but also motor nerve fibers are injured. The loss of toe extensor strength is the only sign of muscle dysfunction in the early stages of the disease. As the disease progresses, even the smallest muscles in the hands and feet get progressively weaker. Muscle atrophy has the potential to alter normal foot motion and pressure distribution.

Weak foot muscles affect joint stability, leading to foot deformities. Foot deformities include hammertoes, cocked toes, equinus deformity, varus deformity, and flat feet are just a few examples. Foot ulceration develops as a result of changes in pressure distribution, shear stress, and friction[25,26,27.]

Excessive sweating, dry skin, cracking, and fissuring are all symptoms of sudomotor dysfunction, which can be brought on by diabetes-related autonomic neuropathy[28].

Peripheral Arterial Disease

Peripheral artery disease is a major contributor to diabetic foot illness (PAD). Chronic, non-healing foot ulcers are a consequence of PAD, which alters the body's normal response to foot ulcerations at times of increased blood flow demand. Consequences of PAD include infection spreading, tissue deterioration, and inadequate delivery of oxygen, nutrients, and medications. The risk of foot amputation is increased by this additional factors[29].

PAD occurs more frequently in people with diabetes than in the general population. Early start, greater severity, rapid progression, or even sex distribution of PAD are also more common in people with diabetes[30]. Twenty percent of individuals with PAD symptoms were also diabetic, according to the Framingham Heart Study[31]. Claudication, or intermittent claudication, is a sign of PAD and is characterized by cramping or painful sensations, most often in the calf muscles but occasionally in the thighs and buttocks. As the condition worsens during walking, the patient is forced to stop, and the condition improves while resting. Ischemic tissue death, gangrene, and critical limb ischemia can all manifest in a limb affected by PAD, and pain can persist even while the patient is at rest[32].

Table 3: Different kinds of debridement for patients with diabetic foot ulcer

Method	Explanation	Advantages	Disadvantages
Sharp or surgical	Clean out the open wound by using a scalpel, tissue nippers, curettes, and curved scissors to remove the callus, dead soft tissue, and damaged bone. Necrotic tissue should be excised as deeply and precisely as required until healthy, bleeding soft tissues and bone are encountered[33].	Cost-effective because it only needs sterile scissors or a scalpel[34].	Requires some level of ability to prevent further bleeding[34].
Mechanical	This technique, widely used to clean wounds before surgical or harsh debridement, involves wet-to-dry dressings, high-pressure irrigation, pulsed lavage, and hydrotherapy [35].	Removes the hardened necrosis	It may remove granulating tissue and is not selective. Patients may experience pain as a result[33].
Autolytic	In a healthy, moist wound environment, this technique naturally occurs. when venous drainage and arterial perfusion are kept at a constant level[17].	It's reasonably priced(34)It can be used on a wound that is excruciatingly painful[17].	It takes time, and treatment may need to be ambiguous in timing[17].
Enzymatic	The sole commercially available formulation in the UK contains both streptokinase and streptodornase (Varidase Topical Wyeth Laboratories). This enzyme is very effective in digesting fibrin, collagen, and elastin, three proteins that are commonly found in necrotic exudate from a wound[36,37].	They can be used directly on necrotic tissue[17].	Streptokinase is contraindicated in people at risk for a MI because it can be systemically absorbed. It costs a lot[17].
Biological	Maggots from a sterile strain of the “green bottle fly (Luciliasericata)” are administered topically and held in place with a net dressing. Larvae have a voracious appetite for necrotic material[38,39] but they avoid freshly formed healthy tissue at all costs.	They distinguish between granulating tissue and necrotic tissue [38].	There may be resistance among patients to take this medication and clinicians. It costs a lot[38]39].

Offloading Technique

Offloading strategies, also known as pressure modulation, are often considered to be the most important aspect of caring for neuropathic ulcers in diabetes patients[40]. Unloading correctly has been proven to aid in the recovery from DFU in recent studies[41].

Despite the widespread use of unloading methods in clinical settings, relatively few researchers have investigated their efficacy in promoting wound healing (Table 4). Ulcer location, ulcer severity, and the patient's physical characteristics all play a role in determining which of these methods to use[42]. So far, total contact casts (TCCs) have shown to be the most effective offloading approach for managing neuropathic DFU[42]. TCC is molded to fit the foot precisely, has little cushioning, and a walking heel for comfort. The cast is designed to take the weight off the ulcer and spread it throughout the whole foot, keeping the injured region safe[42]. Treatment with TCC has been shown to hasten recovery from plantar ulcers compared to standard treatment, according to a randomized controlled trial conducted by Mueller et al.[43]. Histologic examination of ulcer samples also showed that TCC before debridement resulted in better healing as seen by angiogenesis and the formation of granulation tissue than debridement alone, as suggested by the prevalence of inflammatory components[44].

Offloading strategies, also known as pressure modulation, are often considered to be the most important aspect of caring for neuropathic ulcers in diabetes patients[40]. Unloading correctly has been proven to aid in the recovery from DFU in recent studies[41].

Despite the widespread use of unloading methods in clinical settings, relatively few researchers have investigated their efficacy in promoting wound healing (Table 4). Ulcer location, ulcer severity, and the patient's physical characteristics all play a role in determining which of these methods to use[42]. So far, total contact casts (TCCs) have shown to be the most effective offloading approach for managing neuropathic DFU[42]. TCC is molded to fit the foot precisely, has little cushioning, and a walking heel for comfort. The cast is designed to take the weight off the ulcer and spread it throughout the whole foot, keeping the injured region safe[42]. Treatment with TCC has been shown to hasten recovery from plantar ulcers compared to standard treatment, according to a randomized controlled trial conducted by Mueller et al.[43]. Histologic examination of ulcer samples also showed that TCC before debridement resulted in better healing as seen by angiogenesis and the formation of granulation tissue than debridement alone, as suggested by the prevalence of inflammatory components[44].

Table 4: Typical Methods of Offloading

Techniques	Casting Techniques	Footwear related Techniques	Surgical offloading Techniques	Other Techniques
Examples	TCC	Sole or heeled footwear	ATL	Rest
	iTCC	Sandal	Tissue remodeling by infusions of liquid silicon	Crutches, canes, and wheelchairs
	RCW	Insoles	Removing Dead Skin and Calluses	Bracing (ankle-foot orthoses, patella tendon bearing)
	Scotch-cast boots	In-shoe orthoses	Removing the metatarsal head and performing an osteotomy, arthroplasty, exostectomy, or all of the above	Walkers
	Windowed casts	Socks	External fixation	Disposal of Bandages
	Custom splints			Plugs with felted foam/padding

Table 5: Dressings for diabetic foot ulcers: a classification system

Type	Example	Explanation	Advantages	Disadvantages
Hydrocolloids	Duoderm (convatec) Granuflex (convatec) Comfeel (convatec)	The hydrocolloid matrix in such dressings often adheres to a foam or permeable film backing. After making contact with the wound, this matrix forms a gel that helps keep the area moist [45].	Breathable Allows for many days of storage. Evoke autolysis [46]	Use for infected wounds raises concerns Maceration might result. Unpleasant smell [46]

Hydrogels	Aquaform (Maersk Medical) Implant Site Gel (Smith and Nephew) Aquaflo(covidien)	These dressings are comprised of up to 96% water and 4% water-soluble cross-linked polymers (such as starch or carboxymethylcellulose). These dressings may either absorb wound exudate or replenish lost moisture, depending on the quantity of moisture present in the wound. Beads, an amorphous hydrogel, and flat sheets are all available for purchase[45].	Breathable Provide liquids Encourage autolysis[45]	Use for infected wounds raises concerns Maceration might result. Applying to severely exudative wounds[45]
Foams	Allevyn(Smith and Nephew) Cavicare(Smith and Nephew) Biatain(Coloplast) Tegaderm(3M)	Hydrophilic polyurethane foam is a common component of these dressings because of its ability to absorb lesion exudate and therefore sustain the wound surface moist [47].	Superior in absorbing and protecting Can be manipulated [46]	Sporadic dermatitis accompanied by adhesive[46] Bulky[18] It could macerate the skin nearby[18].
Films	Tegaderm (3M) Opsite (Smith and Nephew)	Many types of dressings, such as composite dressings, hydrocolloid dressings, foam dressings, hydrogel sheets, and dressings made of a variety of other materials, all use film as an exterior layer[48,49].	Affordable and easy to manipulate Waterborne microorganisms are blocked, although water vapor and oxygen are let through[50].	The removal process might need to be wet[46]. Don't work well on infected wounds[48,49.] Nonabsorbent If fluid gathers beneath the film, it needs to be drained or the film needs to be replaced[(18)].
Alginates	Dressing with Calcium Alginate (Smith and Nephew Inc., Australia) (ConvaTec's) Kaltostat, Hartman's Sorbalgon (Canada's Derma Sciences Inc.'s) Medihoney	Upon interaction with the lesion, the alginate forms a gel that may be retrieved with the dressings or washed with sterile normal saline. With the additional viscose cushion, shock is absorbed more effectively [51].	Exceptionally absorbing Bacteriostatic Hemostatic Effective in cavities[46]	The removal process might need to be wet[46.]
Silver impregnated	(Smith and Nephew) Acticoat Silver Urgosorb (Urgo)	Due to the obvious use of silver ions, these dressings can be used to heal contaminated wounds [52].	Antiseptic Absorbent[[46] Decreased odor Enhanced pain-related sensations Reduce exudates from wounds[53] Have a long time to get dressed[46]	High price[46]

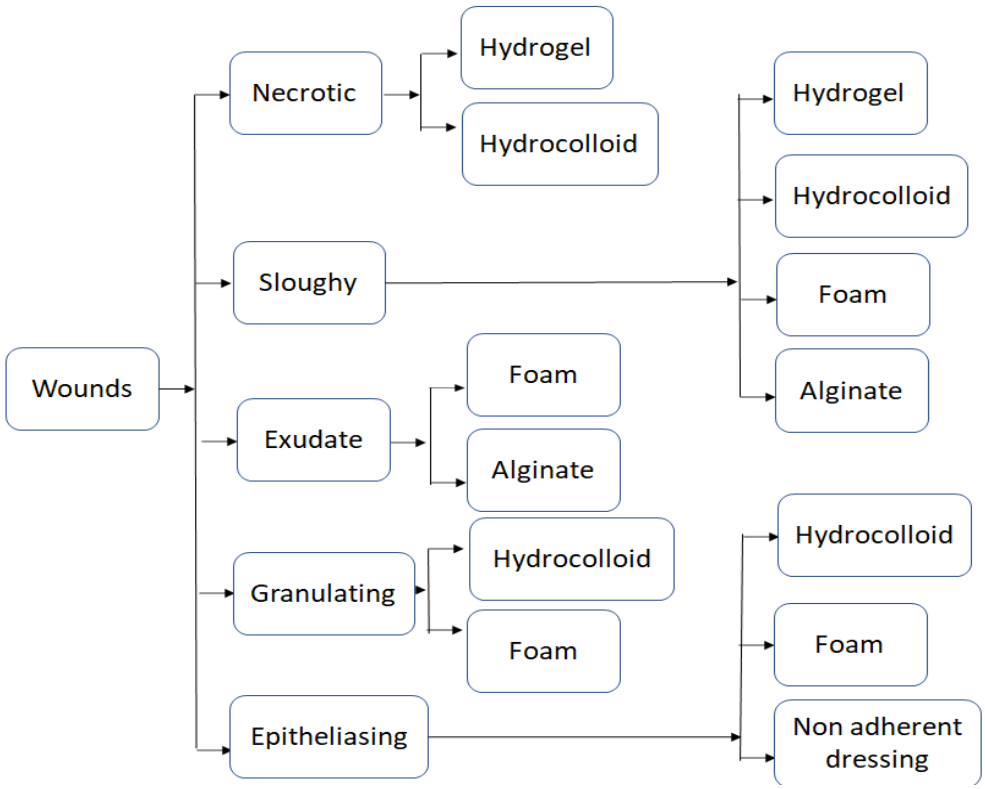

Figure 1: Classification of the several advanced dressing types often used in diabetic foot ulcer treatment [49]

Table 6: Various nonvascular diabetic foot surgery techniques

Type	Explanation
Elective	Patients lacking sensory neuropathy in the periphery as well as at minimal risk for foot ulcers may have surgical procedures to correct deformities including hammertoes, bunions, as well as bone spurs, alleviating their pain.
Prophylactic	Preventing new or recurrent ulcers is a major goal of treatment for people with neuropathy, and these methods are recommended, especially for those with a previous history of this complication (nevertheless absence of active ulceration)
Curative	These treatments are used when offloading and other standard wound care methods have failed to resolve a chronic ulcer's failure to heal or reappearance. These include resecting infected bones as well as joints as a substitute for entire foot resection and other surgical methods aimed at removing locations of consistently increased peak pressure.
Emergent	The goal of these methods is to prevent or significantly reduce the transmission of a critical infection.

Surgery

The prevalence of diabetic foot ulcers (DFU) has grown over the past two decades [53,54], highlighting the need for diabetic foot surgery in its prevention and treatment.

Amputation, non-vascular foot surgery, and vascular foot surgery are common surgical options for DFU rehabilitation. To alleviate plantar pressure, nonvascular foot surgery is classified as either elective, preventative, curative, or emergency.

Advanced Therapies

- ***"Hyperbaric Oxygen Therapy"-***

Some cases of severe, non-healing DFU that have not responded to other treatments may benefit from hyperbaric oxygen therapy (HBOT)[55,56–58]. In hyperbaric oxygen therapy or HBOT, patients get short bursts of pure oxygen delivery many times each day. Hyperbaric oxygen therapy consists of three 30-minute sessions (for a total of 90 minutes) in a hyperbaric chamber, separated by 5-minute breaks[55,59].

But how exactly HBOT works is still a mystery. Hyperbaric oxygen treatment (HBOT) has been shown to promote wound healing by addressing hypoxia, increasing blood flow, reducing edema and cytokines associated with inflammation, and stimulating the proliferation of fibroblasts, collagen formation, as well as angiogenesis[60,61,62,63]. Additionally, HBOT improved the mobilization of bone marrow-derived vasculogenic stem cells and attracted these cells to the injured skin[62].

- ***"Stimulation with Electricity" –***

Based on the available evidence, electrical stimulation (ES) is the most useful supplementary treatment for DFU recuperation. The effectiveness of ES for DFU recovery is now supported by a large body of evidence[64,65,66,67].

Lack of blood flow, infection, and insufficient cellular responses have all been linked to inappropriate wound healing in DFU, although research suggests that ES may help ameliorate these issues [64]. This treatment is a no-frills approach to speeding recovery in DFU patients without any associated risks or high costs.

- ***"Negative Pressure Wound Therapy"–***

A non-invasive technique called negative pressure wound therapy (NPWT) can offer regulated, targeted negative pressure to heal acute and chronic wounds. Sterile polyurethane or PVA foam dressing, devoid of latex, is cut to size for each wound at the bedside and sealed in place with an adhesive drape to prevent air leakage. In most cases, the range of 80–125 mmHg is used for the application of negative pressure, whether it be on a continuous or cyclical basis. Wound fluid is suctioned into a container in the control unit [68,69].

Multiple randomized controlled trials (RCTs) have shown that this method is safe and effective as an adjunct treatment for DFU. Studies have shown that this approach to wound healing improves the healing rate, reduces the time it takes to close the wound, increases the strength of the granulation tissue response, and may reduce the risk of a second amputation compared to the control therapy[69,70,71].

- ***"Bioengineered Skin" –***

Bio-engineered skin (BES) has been used as a nontraditional method of treating DFU in recent decades[72,73,74,75]. This strategy involves injecting a fresh ground material matrix including cellular components to replace the damaged and deteriorating ECM environment and set the patient on a new healing course[76]. Currently, three different BES products are available that may be utilized for DFU[75,77]. These are Derma graft (Advanced Bio healing Inc., La Jolla, CA), Apligraf (Organogenesis Inc., Canton, MA), and Oasis (Cook Biotech, West Lafayette, IN).

BES cells are seeded onto scaffolds for in vitro expansion. Cells can be cultured in vitro, allowing extracellular matrix (ECM) and growth factors secreted by the cells to accumulate in the scaffold. DFU healing may be accelerated by using live cell scaffold cells, which are hypothesized to actively secrete growth factors throughout the repair process[87,88,75,76].

Although BES has many positive effects, they cannot be used to treat DFU by themselves. Peripheral ischemia, a pathogenic feature of DFU, is a major impediment to BES transplantation. As a result, it is generally agreed that BES applications cannot be used without first providing the wound bed with therapy and then performing surgical revascularization and decompression. Infectious-disease prevention and control are also essential to this strategy[36,78].

- ***"Growth Elements"–***

Diabetic ulcers can be effectively treated with growth factors. The manufacture of enzymes, cell division, and migration are all boosted by growth factors. Platelet-derived growth factor (PDGF), epidermis growth factor (EGF), transforming growth factor (TGF)-, TGF-, and insulin-like growth factor (IGF)[92] are some of the growth factors that have been studied. In addition to standard treatment for diabetic foot lesions, recombinant human (rh)-PDGF may be helpful. Neuropathic ulcers reacted better to EGF injections in the form of rh-EGF than ischemic ulcers[80].

Recombinant human platelet-derived growth factor containing becaplermin has been linked to serious adverse events, according to the Food and Drug Administration (FDA). Becaplermin was linked to secondary cancers in both clinical studies and real-world usage. Additional evidence suggests that using three or more tubes of becaplermin gel per year is associated with a higher risk of death from systemic malignancies. Numerous enzyme-based ointments have been used to promote granulation tissue formation and debride sloughy tissues, including fibrinolysin, collagenase, and papain. For debridement purposes, papain-urea is more effective than collagenase[80].

Future Aspects

There has been a dramatic rise in the number of people suffering from complications related to their feet due to diabetes. At the same time, patients have benefited from a flurry of promising new treatments. Hyperbaric oxygen therapy for non-healing diabetic foot diseases entails the complete administration of pure oxygen in sessions daily until the foot ulcer subsides, and negative pressure wound therapy entails the application of negative pressure to close wounds, both acute and chronic. Foamed polyvinyl alcohol is used in this process (both free from latex and sterile). Electric stimulation is another therapeutic method being tested in randomized, placebo-controlled studies.

As a result, scientists and doctors need to put greater effort into developing and expanding these treatments.

CONCLUSION

Diabetic foot ulcers are common and can lead to amputation if not treated promptly, sensibly, and collaboratively across disciplines. Education, blood sugar management, wound cleaning, enhanced dressings, decompression, surgical intervention, and enhanced clinical therapy can all contribute to a speedy and complete recovery from DFU. The high morbidity and danger of catastrophic effects produced by foot ulcers necessitate the adoption of these therapies whenever possible.

REFERENCES

1. Reiber GE, Ledoux WR. Epidemiology of Diabetic Foot Ulcers and Amputations: Evidence for Prevention. In: The Evidence Base for Diabetes Care. Chichester, UK: John Wiley & Sons, Ltd; p. 641–65.
2. J. Apelqvist, K. Bakker, W. H. van Houtum, M. H. Nabuurs-Franssen, N. C. Schaper. International consensus and practical guidelines on the management and the prevention of the diabetic foot. Diabetes Metabolism Research and Review. 2000 Oct 23;16(51):584–92.
3. Shahbazian H, Yazdanpanah L, Latifi SM. Risk assessment of patients with diabetes for foot ulcers according to risk classification consensus of international working group on diabetic foot (IWGDF). Pak J Med Sci. 2013 Apr 30;29(3).
4. Snyder RJ, Hanft JR. Diabetic foot ulcers--effects on QOL, costs, and mortality and the role of standard wound care and advanced-care therapies. Ostomy Wound Manage. 2009 Nov 1;55(11):28–38.
5. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. Ann Med. 2017 Feb 17;49(2):106–16.
6. Nather A, Bee CS, Huak CY, Chew JLL, Lin CB, Neo S, et al. Epidemiology of diabetic foot problems and predictive factors for limb loss. J Diabetes Complications. 2008 Mar;22(2):77–82.
7. Vileikyte L. Diabetic foot ulcers: a quality of life issue. Diabetes Metab Res Rev. 2001 Jul;17(4):246–9.
8. Bartus CL, Margolis DJ. Reducing the incidence of foot ulceration and amputation in diabetes. CurrDiab Rep. 2004 Nov;4(6):413–8.
9. Snyder RJ, Hanft JR. Diabetic foot ulcers--effects on QOL, costs, and mortality and the role of standard wound care and advanced-care therapies. Europe PMC plus. 2009 Nov;55(11):28–38.
10. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. Ann Med. 2017 Feb 17;49(2):106–16.
11. Armstrong DG, Lipsky BA. Diabetic foot infections: stepwise medical and surgical management. Int Wound J. 2004 Jun;1(2):123–32.
12. Yates C, May K, Hale T, Allard B, Rowlings N, Freeman A, et al. Wound Chronicity, Inpatient Care, and Chronic Kidney Disease Predispose to MRSA Infection in Diabetic Foot Ulcers. Diabetes Care. 2009 Oct 1;32(10):1907–9.
13. Gerding DN. Foot Infections in Diabetic Patients: The Role of Anaerobes. Clinical Infectious Diseases. 1995 Jun 1;20(Supplement_2):S283–8.
14. MacDonald YGD, Hait H, Lipsky B, Zasloff M, Holroyd K. Microbiological profile of infected diabetic foot ulcers. Diabetic Medicine. 2002 Dec;19(12):1032–4.
15. Benjamin A. Lipsky. Evidence-based antibiotic therapy of diabetic foot infections. Pathogens and Diseases. 1999 Dec;26(3–4):267–76.
16. Majcher-Peszynska J, Haase G, Saß M, Mundkowski R, Pietsch A, Klammt S, et al. Pharmacokinetics and penetration of linezolid into inflamed soft tissue in diabetic foot infections. Eur J ClinPharmacol. 2008 Nov 25;64(11):1093–100.
17. Frykberg RG, Zgonis T, Armstrong DG, Driver VR, Giurini JM, Kravitz SR, et al. Diabetic Foot Disorders: A Clinical Practice Guideline (2006 Revision). The Journal of Foot and Ankle Surgery. 2006 Sep;45(5):S1–66.
18. Alavi A, Sibbald RG, Mayer D, Goodman L, Botros M, Armstrong DG, et al. Diabetic foot ulcers. J Am AcadDermatol. 2014 Jan;70(1):21.e1-21.e24.
19. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. The Lancet. 2005 Nov;366(9498):1719–24.
20. McEwen LN, Ylitalo KR, Herman WH, Wrobel JS. Prevalence and risk factors for diabetes-related foot complications in Translating Research Into Action for Diabetes (TRIAD). J Diabetes Complications. 2013 Nov;27(6):588–92.
21. Formosa C, Gatt A, Chockalingam N. Diabetic foot complications in Malta: Prevalence of risk factors. The Foot. 2012 Dec;22(4):294–7.
22. Amin N, Doupis J. Diabetic foot disease: From the evaluation of the "foot at risk" to the novel diabetic ulcer treatment modalities. World J Diabetes. 2016;7(7):153.
23. Reiber GE, Vileikyte L, Boyko EJ, del Aguila M, Smith DG, Lavery LA, et al. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. Diabetes Care. 1999 Jan 1;22(1):157–62.
24. Tesfaye S. Clinical Features of Diabetic Polyneuropathy. In: Diabetic Neuropathy. Totowa, NJ: Humana Press; p. 243–57.
25. Nuber GW. Biomechanics of the Foot and Ankle During Gait. Clin Sports Med. 1988 Jan;7(1):1–13.
26. Hazari A, Maiya AG, Shivashankara KN, Agouris I, Monteiro A, Jadhav R, et al. Kinetics and kinematics of diabetic foot in type 2 diabetes mellitus with and without peripheral neuropathy: a systematic review and meta-analysis. Springerplus. 2016 Dec 19;5(1):1819.
27. Frykberg RG, Lavery LA, Pham H, Harvey C, Harkless L, Veves A. Role of Neuropathy and High Foot Pressures in Diabetic Foot Ulceration. Diabetes Care. 1998 Oct 1;21(10):1714–9.
28. Shaw JE, Boulton AJ. The Pathogenesis of Diabetic Foot Problems: An Overview. Diabetes. 1997 Sep 1;46(Supplement_2):S58–61.
29. M. Akbari, Robyn Macsata, Bruce M. Smith, Anton N. Sidawy. Overview of the Diabetic Foot. SeminVasc Surg. 2003;16(1):3–11.
30. Al-Delaimy WK, Merchant AT, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Effect of type 2 diabetes and its duration on the risk of peripheral arterial disease among men. Am J Med. 2004 Feb;116(4):236–40.
31. Murabito JM, D'Agostino RB, Silbershatz H, Wilson PWF. Intermittent Claudication. Circulation. 1997 Jul;96(1):44–9.
32. Nathaniel Clark. Peripheral Arterial Disease in People With Diabetes. Diabetes Care. 2003 Dec 1;26(12):3333–41.
33. Steed DL, Donohoe D, Webster MW, Lindsley L. Effect of extensive debridement and treatment on the healing of diabetic foot ulcers. Diabetic Ulcer Study Group.`. J Am Coll Surg. 1996 Jun 1;183(1):61–4.

34. Edwards J, Stapley S. Debridement of diabetic foot ulcers. Cochrane Database of Systematic Reviews. 2010 Jan 20;

35. Schultz GS, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, et al. Wound bed preparation: a systematic approach to wound management. Wound Repair and Regeneration. 2003 Mar;11(s1):S1–28.

36. Ramundo J, Gray M. Enzymatic Wound Debridement. Journal of Wound, Ostomy and Continence Nursing. 2008 May;35(3):273–80.

37. Langer V, Bhandari PS, Rajagopalan S, Mukherjee MK. Enzymatic debridement of large burn wounds with papain–urea: Is it safe? Med J Armed Forces India. 2013 Apr;69(2):144–50.

38. Grzegorz Jarczyk, Marek Jackowski, Krzysztof Szpila, Grażyna Boszek, Sławomir Kapelaty. Use of Luciliasericata blowfly maggots in the treatment of diabetic feet threatened with amputation. Acta Angiologica. 2008 Apr 30;14(2):42–55.

39. Bowling FL, Salgami E v., Boulton AJM. Larval Therapy: A Novel Treatment in Eliminating Methicillin-Resistant *Staphylococcus aureus* From Diabetic Foot Ulcers. Diabetes Care. 2007 Feb 1;30(2):370–1.

40. Armstrong DG, Nguyen HC, Lavery LA, van Schie CHM, Boulton AJM, Harkless LB. Off-Loading the Diabetic Foot Wound. Diabetes Care. 2001 Jun 1;24(6):1019–22.

41. Peter R. Cavanagh. Off-loading the Diabetic Foot for Ulcer Prevention and Healing. J Am Podiatr Med Assoc. 2010 Sep;100(5):360–8.

42. Armstrong DG, Lavery LA, Nixon BP, Boulton AJM. It's Not What You Put On, but What You Take Off: Techniques for Debriding and Off-Loading the Diabetic Foot Wound. Clinical Infectious Diseases. 2004 Aug 1;39(Supplement_2):S92–9.

43. Mueller MJ, Diamond JE, Sinacore DR, Delitto A, Blair VP, Drury DA, et al. Total Contact Casting in Treatment of Diabetic Plantar Ulcers: Controlled Clinical Trial. Diabetes Care. 1989 Jun 1;12(6):384–8.

44. Piaggesi A, Viacava P, Rizzo L, Naccarato G, Baccetti F, Romanelli M, et al. Semiquantitative Analysis of the Histopathological Features of the Neuropathic Foot Ulcer. Diabetes Care. 2003 Nov 1;26(11):3123–8.

45. Dumville JC, Deshpande S, O'Meara S, Speak K. Hydrocolloid dressings for healing diabetic foot ulcers. Cochrane Database of Systematic Reviews. 2013 Aug 6;

46. Hilton JR, Williams DT, Beuker B, Miller DR, Harding KG. Wound Dressings in Diabetic Foot Disease. Clinical Infectious Diseases. 2004 Aug 1;39(Supplement_2):S100–3.

47. Dumville JC, Deshpande S, O'Meara S, Speak K. Foam dressings for healing diabetic foot ulcers. Cochrane Database of Systematic Reviews. 2013 Jun 6;

48. Thomas DR, Goode PS, LaMaster K, Tennyson T, Parnell LK. A comparison of an opaque foam dressing versus a transparent film dressing in the management of skin tears in institutionalized subjects. Ostomy Wound Manage. 1999 Jun;45(6):22–4, 27–8.

49. Moura LIF, Dias AMA, Carvalho E, de Sousa HC. Recent advances on the development of wound dressings for diabetic foot ulcer treatment—A review. ActaBiomater. 2013 Jul;9(7):7093–114.

50. Dumville JC, O'Meara S, Deshpande S, Speak K. Alginate dressings for healing diabetic foot ulcers. In: Dumville JC, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2012.

51. Carter MJ, Tingley-Kelley K, Warriner RA. Silver treatments and silver-impregnated dressings for the healing of leg wounds and ulcers: A systematic review and meta-analysis. J Am AcadDermatol. 2010 Oct;63(4):668–79.

52. Armstrong DG, Lavery LA, Stern S, Harkless LB. Is prophylactic diabetic foot surgery dangerous? The Journal of Foot and Ankle Surgery. 1996 Nov;35(6):585–9.

53. Capobianco CM, Stapleton JJ, Zgonis T. Soft Tissue Reconstruction Pyramid in the Diabetic Foot. Foot Ankle Spec. 2010 Oct 7;3(5):241–8.

54. Armstrong DG, Frykberg RG. Classifying diabetic foot surgery: toward a rational definition. Diabetic Medicine. 2003 Apr;20(4):329–31.

55. Strauss MB. Hyperbaric Oxygen as an Intervention for Managing Wound Hypoxia: Its Role and Usefulness in Diabetic Foot Wounds. Foot Ankle Int. 2005 Jan 9;26(1):15–8.

56. Cianci P. Advances in the treatment of the diabetic foot: Is there a role for adjunctive hyperbaric oxygen therapy? Wound Repair and Regeneration. 2004 Jan;12(1):2–10.

57. Landau Z, Sommer A, Miller EB. Topical hyperbaric oxygen and low-energy laser for the treatment of chronic ulcers. Eur J Intern Med. 2006 Jul;17(4):272–5.

58. Barnes RC. Point: Hyperbaric Oxygen Is Beneficial for Diabetic Foot Wounds. Clinical Infectious Diseases. 2006 Jul 15;43(2):188–92.

59. Gill AL, Bell CNA. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. QJM. 2004 Jul 1;97(7):385–95.

60. Al-Waili NS, Butler GJ. Effects of Hyperbaric Oxygen on Inflammatory Response to Wound and Trauma: Possible Mechanism of Action. The Scientific World JOURNAL. 2006;6:425–41.

61. Thom SR. Hyperbaric Oxygen: Its Mechanisms and Efficacy. PlastReconstr Surg. 2011 Jan;127:131S-141S.

62. Niinikoski JHA. Clinical Hyperbaric Oxygen Therapy, Wound Perfusion, and Transcutaneous Oximetry. World J Surg. 2004 Mar 1;28(3):307–11.

63. Peters EJ, Lavery LA, Armstrong DG, Fleischli JG. Electric stimulation as an adjunct to heal diabetic foot ulcers: A randomized clinical trial. Arch Phys Med Rehabil. 2001 Jun;82(6):721–5.

64. PETROFSKY JS, LAWSON D, BERK L, SUH H. Enhanced healing of diabetic foot ulcers using local heat and electrical stimulation for 30 min three times per week. J Diabetes. 2010 Mar;2(1):41–6.

65. Thomas C.M, Sven V Erikson, Mats Malam. Electrical Nerve Stimulation Improves Healing of Diabetic Ulcers. Little , Brown and Company. 1992;328–31.

66. Baker LL, Chambers R, DeMuth SK, Villar F. Effects of Electrical Stimulation on Wound Healing in Patients With Diabetic Ulcers. Diabetes Care. 1997 Mar 1;20(3):405–12.

67. Vikatmaa P, Juutilainen V, Kuukasjärvi P, Malmivaara A. Negative Pressure Wound Therapy: a Systematic Review on

Effectiveness and Safety. European Journal of Vascular and Endovascular Surgery. 2008 Oct;36(4):438–48.

68. Armstrong DG, Lavery LA. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. The Lancet. 2005 Nov;366(9498):1704–10.

69. Sadat U, Chang G, Noorani A, Walsh SR, Hayes PD, Varty K. Efficacy of TNP on lower limb wounds: a meta-analysis. J Wound Care. 2008 Jan;17(1):45–8.

70. Ubbink DT, Westerbos SJ, Nelson EA, Vermeulen H. A systematic review of topical negative pressure therapy for acute and chronic wounds. British Journal of Surgery. 2008 Apr 29;95(6):685–92.

71. Kim PJ, Heilala M, Steinberg JS, Weinraub GM. Bioengineered Alternative Tissues and Hyperbaric Oxygen in Lower Extremity Wound Healing. ClinPodiatr Med Surg. 2007 Jul;24(3):529–46.

72. Teng YJ, Li YP, Wang JW, Yang KH, Zhang YC, Wang YJ, et al. Bioengineered skin in diabetic foot ulcers. Diabetes ObesMetab. 2010 Apr;12(4):307–15.

73. Bello YM, Falabella AF, Eaglstein WH. Tissue-Engineered Skin. Am J ClinDermatol. 2001;2(5):305–13.

74. Richmond NA, Vivas AC, Kirsner RS. Topical and Biologic Therapies for Diabetic Foot Ulcers. Medical Clinics of North America. 2013 Sep;97(5):883–98.

75. Futrega K, King M, Lott WB, Doran MR. Treating the whole not the hole: necessary coupling of technologies for diabetic foot ulcer treatment. Trends Mol Med. 2014 Mar;20(3):137–42.

76. Kirsner RS, Warriner R, Michela M, Stasik L, Freeman K. Advanced Biological Therapies for Diabetic Foot Ulcers. Arch Dermatol. 2010 Aug 1;146(8):32-37.

77. Serra R, Rizzuto A, Rossi A, Perri P, Barbetta A, Abdalla K, et al. Skin grafting for the treatment of chronic leg ulcers - a systematic review in evidence-based medicine. Int Wound J. 2017 Feb;14(1):149–57.

78. Fitton AR, Drew P, Dickson WA. The use of a bilaminate artificial skin substitute (IntegraTM) in acute resurfacing of burns: an early experience. Br J Plast Surg. 2001 May;54(3):208–12.

79. Hogge J, Krasner D, Nguyen H, Harkless L, Armstrong D. The potential benefits of advanced therapeutic modalities in the treatment of diabetic foot wounds. J Am Podiatr Med Assoc. 2000 Feb 1;90(2):57–65.

80. Knighton DR, Ciresi KF, Fiegel VD, Austin LL, Butler EL. Classification and treatment of chronic nonhealing wounds. Successful treatment with autologous platelet-derived wound healing factors (PDWHF). Ann Surg. 1986 Sep;204(3):322–30.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.